CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214429Orig1s000

PRODUCT QUALITY REVIEW(S)

MEMORANDUM

Date: June 25, 2021

To: Alison Rodgers, PM, Division of Anti-Infectives (DAI)

From: Dorota Matecka, Application Technical Lead (ATL),
Office of Pharmaceutical Quality (OPQ)

Re: **NDA 214429 - Resubmission dated May 18, 2021 (SDN # 0035)**

Subject: **OPQ Assessment # 2**

The original NDA was submitted on March 12, 2021 by sanofi-aventis U.S. LLC (Sanofi) and was issued a Complete Response (CR) letter on November 12, 2020 due to the lack of the final labeling agreements. The ownership of the NDA has since changed to Drugs for Neglected Diseases initiative (DNDi).

The overall Product Quality information was found acceptable in the previous review cycle (refer to the OPQ Integrated Quality Assessment # 1, dated August 12, 2020, in DARRTS). There have been no Product Quality changes or new information included in the current NDA resubmission. In the previous review cycle, the Applicant has agreed to develop via a Post Marketing Commitment (PMC) study, the [redacted] (b) (4) procedure to designate it as a first GMP step in the manufacturing process of the fexinidazole drug substance. The protocol for this study was submitted in the amendment dated February 1, 2021 (SDN # 0032). This submission was evaluated in the current review cycle and found acceptable (refer to the Drug Substance Memorandum, attached below). The draft labeling provided in the NDA resubmission includes only minor revisions to the previously agreed version (refer to the Labeling Memorandum, attached below). In addition, all manufacturing and testing facilities remain acceptable and the overall "Approve" recommendation was re-entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on June 22, 2021.

Therefore, this NDA continues to be recommended for **Approval** by the OPQ team. The following PMC study and timelines should be included in the action letter for this NDA:

Develop a procedure for the [redacted] (b) (4) *and establish it as a first GMP step in the manufacturing process for fexinidazole drug substance.*

Interim Report Submission: February 1, 2022
Final Report Submission: August 1, 2022

The above change in the manufacturing process of fexinidazole drug substance will be submitted as a prior-approval supplement to the NDA.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 17, 2021

FROM: Raymond P. Frankewich, Ph.D., Review Chemist, CDER / OPQ / ONDP / DNDAPI / Branch 1

THROUGH: Paresma R. Patel, Ph.D., Branch Chief, CDER / OPQ / ONDP / DNDAPI / Branch 1

SUBJECT: Protocol to address Post Marketing Commitment for NDA 214429 for Fexinidazole (b) (4) (fexinidazole) tablet 600 mg

TO: NDA 214429

A resubmission dated May 18, 2021 was made to NDA 214429 by applicant Sanofi-Aventis U.S. LLC, following a Complete Response (CR) letter dated November 12, 2020. The resubmission did not address CMC issues or contain CMC data, but it did prompt an evaluation of any amendment containing CMC information that have been submitted since the CR letter.

In a submission dated August 3, 2020 (SDN 21, Seq. no. 0021), the applicant Sanofi-Aventis agreed to the (b) (4) as the first step of the manufacturing process of fexinidazole drug substance to be implemented as a Postmarketing Commitment (PMC) subsequently submitted as a prior-approval supplement to the NDA. Sanofi agreed with the PMC timelines as proposed by the Agency (reference is made to the Drug Substance Review for this NDA finalized on August 4, 2020, and the Minutes from the Late Cycle Meeting, finalized on October 15, 2020). The timelines are as follows:

Protocol Submission:	February 01, 2021
Interim Report Submission:	February 01, 2022
Final Report Submission:	August 01, 2022

ary

(b) (4)

(b) (4)

implementing the revised manufacture process for fexinidazole. The interim and final report submission are pending, and should be communicated as part of the final PMC to the applicant.

Protocol Submission: February 01, 2021 (***Adequate***)
Interim Report Submission: February 01, 2022
Final Report Submission: August 01, 2022

Raymond Frankewich

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Paresma Patel

Digitally signed by Paresma Patel
Date: 6/21/2021 12:30:52PM
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Memo

From: **George Lunn, Ph.D.**

To: **Dorota Matecka, Ph.D.**

Date: **June 21, 2021**

Subject: **NDA 214429 Resubmission**

There are no CMC changes in the resubmission. There do not appear to be any changes in Sections 3, 11, and 16 of the Prescribing Instructions. The storage statement of (b) (4) (b) (4) in the revised Prescribing Instructions.

At the end of the Prescribing Instructions it now states:

Manufactured for:
Drugs for Neglected Diseases *initiative*
15 Chemin Camille-Vidart
1202 Geneva
Switzerland

Distributed by:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

Previously it stated "Distributed by: sanofi-aventis… " with no mention of Drugs for Neglected Diseases.

For the blister packs a similar change is made. Additionally in the blister packs, (b) (4) becomes "Store below 30°C (86°F)" and the name "Fexinidazole (b) (4) becomes "Fexinidazole Tablets" and the banner stating (b) (4) is dropped.

These changes are all acceptable from the CMC perspective.

George Lunn

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Dorota Matecka

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Date: 6/25/2021 03:00:15PM
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DOROTA M MATECKA
06/25/2021 05:38:40 PM

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RECOMMENDATION

☐ Approval
☒ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214429
Assessment # 1

Drug Product Name	Fexinidazole Tablets*
Dosage Form	Tablets
Strength	600 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	sanofi-aventis U.S. LLC
US agent, if applicable	N/A

**No proprietary name proposed*

Submission(s) Assessed	Document Date	Discipline(s) Affected
0001	March 12, 2020	All
0009	May 11, 2020	Drug Product, Biopharmaceutics
0012	June 15, 2020	Drug Substance, Environmental Analysis, Biopharmaceutics
0013	June 19, 2020	Drug Substance
0015	July 7, 2020	Drug Product, Labeling
0019	July 10, 2020	Drug Substance
0020	July 17, 2020	Drug Substance
0021	August 3, 2020	Drug Substance

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Raymond Frankewich	Ali Al Hakim
Drug Product	George Lunn	Thomas Oliver
Manufacturing	Satheesh Podaralla	Steven Frisbee
Microbiology	Satheesh Podaralla	Steven Frisbee
Biopharmaceutics	Churg Chan (Stella)	Elsbeth Chikhale
Environmental Analysis	Raanan Bloom (*refer to the Drug Product Review)*	
Laboratory (OTR)	N/A	
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

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QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)		N/A*	
	III				N/A*	

** Sufficient information provided in the NDA*

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	110365	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

FDA U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, fexinidazole tablets. All information requests and review issues have been addressed and there are no pending approvability issues at this time. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on July 31, 2020. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

The following CMC post-marketing commitment (PMC) has been established and should be included in the action letter for this NDA:

PMC Study

Develop a procedure for the (b) (4) *and establish it as a first GMP step in the manufacturing process for fexinidazole drug substance.*

PMC Timelines

Protocol Submission: February 1, 2021
Interim Report Submission: February 1, 2022
Final Report Submission: August 1, 2022

The above change in the manufacturing process of fexinidazole drug substance will be submitted as a prior-approval supplement to the NDA.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Fexinidazole, a 2-substituted 5-nitroimidazole, is a broad-spectrum antiprotozoal, which belongs to a wider class of nitroimidazole anti-infective agents (such as benznidazole and metronidazole). Fexinidazole is indicated for the treatment of Human African trypanosomiasis (HAT), or sleeping sickness, which is one of the most neglected tropical diseases, considered endemic in remote areas of Sub-Saharan African countries.

The proposed drug product, fexinidazole tablet, 600 mg, is an immediate-release tablet. The intended therapeutic dosing regimen is a once daily dose for 10 days with food.

Proposed Indication(s) including Intended Patient Population	Fexinidazole tablets is an antiprotozoal indicated for the treatment of both first-stage (hemolymphatic) and second-stage (meningoencephalitic) of human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* in adult and pediatric patients (6 years and older and weighing at least 20 kg to less than 35kg).
Duration of Treatment	10 days (*see package insert for details regarding treatment and daily dosage*)
Maximum Daily Dose	1800 mg (3 tablets)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

Fexinidazole drug substance, a 2-substituted 5-nitroimidazole, belongs to a wider class of nitroimidazole anti-infective agents, and is considered a New Molecular Entity. The supporting CMC information for fexinidazole drug substance has been provided in Module 3 of the NDA.

Fexinidazole is a yellow, crystalline, non-hygroscopic powder, which is practically insoluble in water, sparingly soluble in acetone and acetonitrile, very slightly soluble in ethanol, and slightly soluble in methanol. The chemical structure of fexinidazole does not contain any chiral center; therefore, fexinidazole does not exhibit any optically active isomers. Fexinidazole drug substance is produced as a base (not a salt) with only one polymorphic form identified so far (Form 1).

The manufacturing process of fexinidazole drug substance includes (b) (4)

The original NDA submission contained (b) (4)

During the review, in response to the FDA comments and recommendations

(b) (4) the Applicant indicated that (b) (4) in the fexinidazole manufacturing process. In response to FDA recommendation, the Applicant has agreed to develop (b) (4) and establish it as a first GMP step in the manufacturing process for fexinidazole drug substance via a Post Marketing Commitment (PMC) study. The Applicant also agreed that after completing the PMC study, the change in the manufacturing process of fexinidazole drug substance would be implemented via a prior-approval supplement to the NDA. In addition, (b) (4)

The drug substance specification includes quality attributes such as appearance, identification, loss on drying, (b) (4), related substances, residual solvents, assay, microbiological purity, and particle size distribution. Batch analysis results provided for representative batches of the drug substance have been found consistent thus indicating that adequate controls are in place in the manufacturing process. Several FDA comments regarding the assay calculation and the analytical procedures used for impurities and residual solvents were addressed satisfactorily by the Applicant, and the overall specification (tests, analytical procedures, and acceptance criteria) has been found adequate.

Fexinidazole drug substance is packaged in (b) (4) complies with relevant food contact regulations and USP physicochemical and biological reactivity tests. The retest period for fexinidazole drug substance is (b) (4) months when stored in its original container at (b) (4)

The overall information submitted in the NDA for the drug substance was found adequate (*refer to the Drug Substance Review for details*).

Drug Product: Adequate

The drug product, fexinidazole tablets, 600 mg, are pale yellow, round, 13 mm diameter, 7 mm thick, biconvex tablets, debossed with 4512 on one side. The tablets are packaged in blister packs made of aluminum foil with peel-able aluminum foil lidding.

The drug product formulation contains conventional excipients of compendial grade. The specification includes appropriate for the proposed dosage form quality attributes, such as appearance,

identification, assay, related substances, uniformity of dosage form, dissolution, microbial limits, and [redacted]. The results of batch analysis for the drug product representative batches have been found consistent. The levels of impurities observed in drug product batches are quite low and the proposed acceptance criterion of NMT [redacted]% for each individual impurity was found acceptable. However, the originally proposed acceptance criterion for total impurities was revised from NMT [redacted]% to NMT [redacted]% at the FDA request. The drug product specification, including the analytical procedures and acceptance criteria, as revised, have been found adequate (*refer to the Biopharmaceutics Review and Manufacturing Integrated Assessment regarding the dissolution and microbial limits tests, respectively*).

The stability information submitted in the NDA include 48 months of satisfactory stability data for three representative batches stored at 30°C/75% RH with no out of specification results and no obvious trends. Therefore, the 48-month expiration dating was granted for the drug product to be stored below 30 deg C.

The Applicant has submitted a claim of categorical exclusion and a statement of no extraordinary circumstances. The cited categorical exclusion, 21 CFR 25.31(b), is appropriate for the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is acceptable.

The overall drug product information submitted in the NDA was found adequate (*refer to the Drug Product Review for details*).

Labeling: Adequate

The proposed labeling and container labels include the necessary product quality related information and have been found generally acceptable. Several minor revisions in the relevant sections (Sections 3, 11 and 16) of the Prescribing Information have been recommended (*for details refer to the Labeling Review*).

Manufacturing: Adequate

The drug product manufacturing process consists of the following major unit operations: [redacted] packaging and labeling. Extensive developmental studies were conducted to optimize critical process parameters (CPPs) and establish appropriate controls throughout the process. All clinical and scale up batches meet the established in-process specifications. There are no API overages and no reprocessing employed

in the manufacturing process of current and future batches. In addition, adequate microbiological controls are established for the drug product.

The drug substance is manufactured at [redacted] and the drug product is manufactured by [redacted] Based on manufacturing risks identified in the NDA review, robustness of manufacturing process, scale up, and the use of on-site controls to ensure CQAs (including [redacted]), a pre-approval inspection of the drug product site was not recommended.

Both the manufacturing process and the facilities have been found adequate (*refer to the Manufacturing Integrated Assessment for further details),* and the overall manufacturing recommendation of "Approve" was entered into Panorama on July 31, 2020.

Biopharmaceutics: Adequate

The biopharmaceutics review focused on the assessment of the proposed dissolution test (analytical procedure and acceptance criterion), which is part of the routine quality control testing for fexinidazole tablets at release and during shelf-life. The dissolution method was found acceptable and the proposed acceptance criterion was revised at the FDA recommendation, as follows:

USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion
II (Paddle)	75 RPM	0.1 N HCl with 3% w/v SLS	2000 mL/ 37.0 ± 0.5 °C	Q= [redacted]% at 60 minutes

In addition, bridging of formulations was also part of the biopharmaceutics assessment. Drug product development began in [redacted] for clinical studies and moved to [redacted] to scale up commercial drug product manufacturing. The Applicant conducted a bioequivalence study (DNDiHATFEX008) to bridge the [redacted] formulations (that is being reviewed by the Office of Clinical Pharmacology) and performed comparative dissolution studies. The results of the comparative dissolution studies were found acceptable *(for details refer to the Biopharmaceutics Review*).

Microbiology (if applicable): Adequate

N/A – oral dosage form (*refer to the Manufacturing Integrated Assessment for details*)

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	Formulation Raw materials Process parameters Scale/equipment Site	Low	(b) (4)	Acceptable	
Content uniformity	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	
Physical stability	Formulation Raw materials Process parameters Scale/equipment Site	Medium		Acceptable	
Microbial limits	Formulation Raw materials Process parameters Scale/equipment Site	Low		Acceptable	
Dissolution	Formulation Raw materials Process parameters Scale/equipment Site	Medium		Acceptable	

Application Technical Lead Name and Date:
Dorota Matecka, 8/12/2020

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

Note: The Established Name is Fexinidazole Tablets based on the following reasoning.

21 CFR 299.4

(b) The term established name is defined in section 502(e)(3) of the act as (1) an official name designated pursuant to section 508 of the act; (2) if no such official name has been designated for the drug and the drug is an article recognized in an official compendium, then the official title thereof in such compendium; and (3) if neither paragraphs (b) (1) or (2) of this section applies, then the common or usual name of the drug.

From:
https://www.fda.gov/drugs/data-standards-manual-monographs/use-drug-name-terms-policy

Established Name: The designated FDA Official name, the Compendial name, the USAN Council name or the common or usual name (section 502(e)(3) of the Act and 21 CFR 299.4). Ordinarily, the established name of a drug will be the compendial name. However, FDA may designate an established name in cases where a monograph does not exist.

There is no USP monograph for fexinidazole but if there was a monograph it would undoubtedly be called "Fexinidazole Tablets" so I would agree that the Established Name is "Fexinidazole tablets".

Also from 299.4: Section 502(e) of the act … prescribes that the labeling of a drug must bear its established name, if there is one, to the exclusion of any other nonproprietary name (except the applicable systematic chemical name or the chemical formula)

Which I think you could read as requiring "Fexinidazole Tablets" to be used throughout the PI.

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments

Product Title in Highlights		
Proprietary name	None	Adequate
Established name(s)	Fexinidazole	Should be fexinidazole tablets
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 600 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	No score	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	The tablets should not be broken or crushed	Acceptable to CMC but would defer to clinical. Tablets are photosensitive and might turn brown when crushed. No data to support crushing in NDA.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	600 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not a salt	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	pale-yellow, round, biconvex tablets debossed with "4512" on one side	Adequate. Suggest change to "Tablets: 600 mg of fexinidazole as pale-yellow, round, biconvex tablets debossed with "4512" on one side"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	No score	Adequate
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Fexinidazole	Adequate
Dosage form(s) and route(s) of administration	Tablets	Adequate. Tablets are for oral use but it is not necessary to state this.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Not a salt	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Statement of being sterile (if applicable)	NA	
Pharmacological/ therapeutic class	(b) (4)	Adequate but would defer to Clin Micro

Chemical name, structural formula, molecular weight	1-Methyl-2-{[4-(methylthio)phenoxy]methyl}-5-nitro-1H-imidazole.[1] molecular formula is $C_{12}H_{13}N_3O_3S$ and the molecular weight is 279.3 g/mol. Structural formula provided.	Adequate. Remove capital M from Methyl
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa or pH)	Yellow powder practically insoluble in water, sparingly soluble in acetone and acetonitrile, very slightly soluble in ethanol and slightly soluble in methanol	Adequate.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None	Adequate.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablet	Adequate
Strength(s) in metric system	600 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Dose pack of 24 tablets and dose pack of 14 tablets	Generally adequate. Suggest term "blister pack". Number of tablets may change depending on dosing recommendations.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	pale-yellow, round, biconvex tablets debossed with "4512" on one side	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	No score	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store in the original package in order to protect from light and moisture	Adequate, supported by data in NDA
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	No desiccant	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	(b) (4)	Should certainly be (b) (4) (b) (4) Could be "Store up to 30°C (86°F)"
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	
Include information about child-resistant packaging	The applicant claims that the dosepak is child resistant (3.2.P.7, page 4) but no evidence is supplied to support this statement.	It is acceptable to not state that the package is child resistant.

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured by: (b) (4)	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

Acceptable from a CMC perspective. The suggestions above have been incorporated in the SharePoint label.

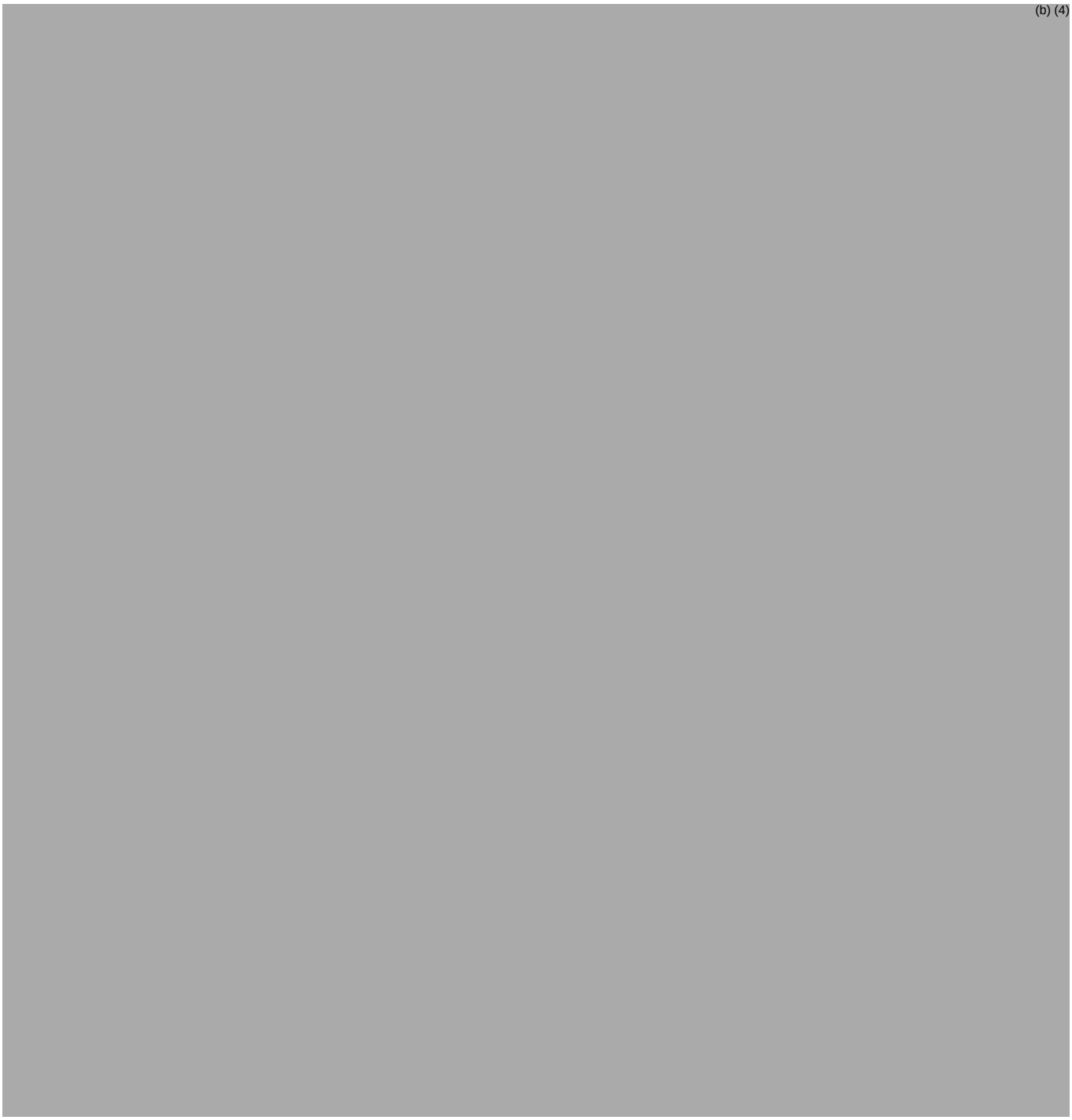
3.0 CARTON AND CONTAINER LABELING

Note that additional information is provided in the Amendment of 7/7/20. The container-closure system is child-resistant and complies with 16 CFR 1700. An instructional video is provided showing that a button is pushed and then the blister card may be slid out from the carton. The blisters can then be opened conventionally. The carton and container remain together and so it is acceptable to only have the lot number and expiration on the carton (not on the blister pack).

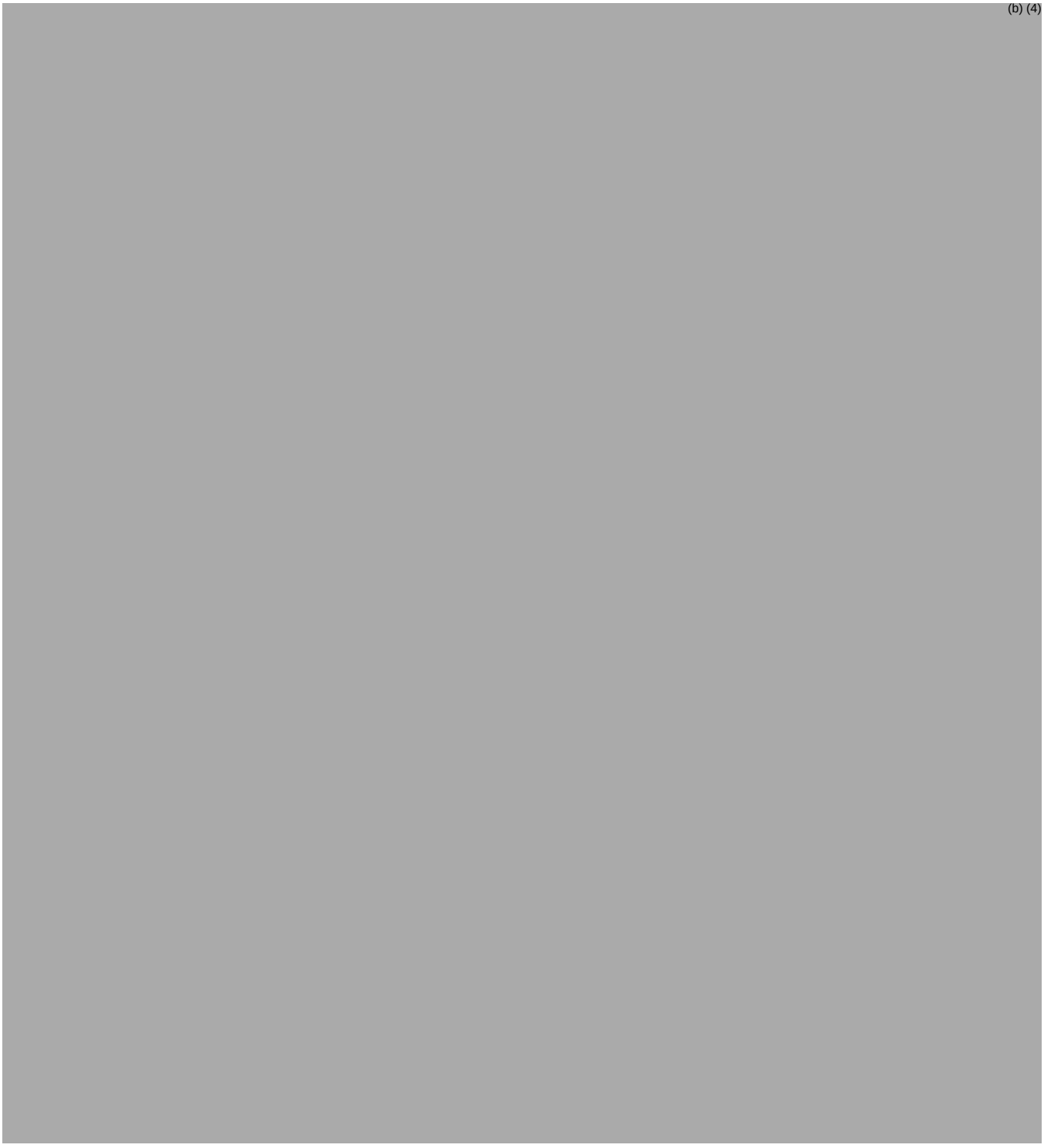
3.1 Container Label

The tablets are packaged in 14 and 24 count blisters that are placed in cartons.

The 14 count blister is as follows.



The 24 count blister is as follows.



The text on the cartons and blisters is as follows.

14 count blister (24 count is similar except it's 3 tablets then 2 tablets)

Treatment Days 1 to 4:

TAKE 2 TABLETS ONCE DAILY WITH FOOD
AT THE SAME TIME EACH DAY

Treatment Days 5 to 10:

TAKE 1 TABLET ONCE DAILY WITH FOOD
AT THE SAME TIME EACH DAY

Each tablet contains 600 mg of fexinidazole.

Dosage: Take once daily for 10 days with food at the same time each day.

Do not break or crush tablets.

Storage: (b) (4) Store in original package to protect from light and moisture.

Warning: Keep out of the reach of children.

14 Count Carton

The 24 count carton is similar except that it has 3 tablets/2 tablets and states "for adults and children weighing 35 kg or more". Both cartons have a space for Lot and Expiry.

Opening Instructions:

Press and hold down

button while pulling out

medication card.

NDC XXXX—XXXX—XX Rx only

Fexinidazole

Tablets

600 mg per tablet

10-Day Dose Pack

for children 6 years and older

weighing 20 to less than 35 kg

DISPENSE ONLY IN ORIGINAL PACKAGE

14 tablets SANOFI

TAKE THE TREATMENT

FOR 10 DAYS

Record your dose as you take it each day:

[Check symbol]

1 Two tablets	5 One tablet
2 Two tablets	6 One tablet
2 Two tablets	7 One tablet
4 Two tablets	8 One tablet
	9 One tablet
	10 One tablet

Each tablet contains 600 mg of fexinidazole.

Dosage: Take once daily for 10 days with food at the same time each day. Do not break or crush tablets.

Storage: (b) (4) Store in original package to protect from light and moisture.

Warning: Keep out of the reach of children.

[Bar Code]

Note: Review below refers to 14 tablet pack. Differences in 24 tablet pack shown in green.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Fexinidazole Tablets	Adequate
Dosage strength	600 mg per tablet	Adequate but would defer to DMEPA if they want "600 mg"
Route of administration	NA	Administration is oral but that does not need to be stated
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	
Net contents (e.g. tablet count)	14 Tablets 24 tablets	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	Present	Adequate
Lot number and expiration date	Present. Expiration format is YYYY-MM	Adequate but would defer to DMEPA if they want a different format
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Storage: (b) (4) Store in original package to protect from light and moisture.	Adequate but should be 30°C (86°F).
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	Blisters are labeled "Two tablets" and "One tablet" Blisters are labeled "Three tablets" and "Two tablets"	Adequate

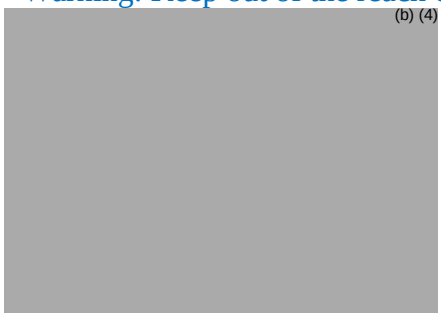
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Bar code	Present on carton	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	(b) (4)	Adequate
(b) (4)		
No text on Ferrule and Cap overseal	NA	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	
And others, if space is available	Do not break or crush tablets. Warning: Keep out of the reach of children. Dispense only in original package. Opening Instructions: Press and hold down button while pulling out medication card.	Adequate

Blister Pack

These are pictured separately from the carton but it appears that the carton and the blister pack will work together as one unit. The following information is provided on both the carton and the blister pack.

Each tablet contains 600 mg of fexinidazole.
Dosage: Take once daily for 10 days with food at the same time each day. Do not break or crush tablets.
Storage: (b) (4) Store in original package to protect from light and moisture.
Warning: Keep out of the reach of children.



However, much of the information, such as the drug name, strength, storage conditions, lot number, expiration date, is not repeated on the blister pack.

The following information does appear on the blister pack.

Analogous wording appears on the 24 tablet blister package.

Assessment of Carton and Container Labeling: *{Adequate}*

The carton and blister pack work together to provide a child-resistant package that conforms to 16 CFR 1700. Generally, the carton and blister pack are acceptable. The following comment could be conveyed to the applicant.

Storage statement should be "Store up to 30°C (86°F)".

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: George Lunn, Ph.D.

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Thomas Oliver, Ph.D.

[i] [Module 2.3.S Drug substance, Section 2.3.S.1.1 Nomenclature]

George Lunn

Digitally signed by George Lunn
Date: 8/10/2020 09:46:15AM
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Thomas Oliver

Digitally signed by Thomas Oliver
Date: 8/10/2020 10:04:55AM
GUID: 508da71f00029ed4697700cee3d31ca0
Comments: Just signed label review George! Thank you!

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	Immediate-Release Oral Tablet
NDA Number	214429
Assessment Cycle Number	1
Drug Product Name/ Strength	Fexinidazole; 600 mg
Route of Administration	Oral
Applicant Name	Sanofi-Aventis US LLC
Therapeutic Classification/ OND Division	DAI
RLD/RS Number	N/A
Proposed Indication	First-stage and second-stage human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense*

Assessment Recommendation: **Adequate**

Background:
Sanofi-Aventis US LLC is seeking approval under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Fexinidazole Tablets, 600 mg, for the treatment of first-stage and second-stage human African trypanosomiasis due to *Trypanosoma brucei gambiense*.

Bridging of Formulations:
Drug product development began in (b) (4) for clinical studies and moved to (b) (4) to scale up commercial drug product manufacturing. The Applicant conducted a bioequivalence study (DNDiHATFEX008) to bridge the (b) (4) formulations. The Office of Clinical Pharmacology will review the results of this study.

Assessment Summary:
For the routine quality control testing of Fexinidazole 600 mg Tablets at batch release and during shelf-life, the following dissolution method and revised acceptance criterion, shown in the table below, are found acceptable:

USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion
II (Paddle)	75 RPM	0.1 N HCl with 3% w/v SLS	2000 mL/ 37.0 ± 0.5 °C	Q= (b) (4)% at 60 minutes

Overall Review Recommendation:
From a Biopharmaceutics perspective, **NDA 214429** for Fexinidazole 600 mg Tablets is recommended for **approval**.

List Submissions being assessed:

Document(s) Assessed	Date Received
SDN-1 (Original NDA Submission)	3/12/2020
SDN-9 (Response to Quality Information Request)	5/11/2020
SDN-12 (Response to Quality Information Request)	6/15/2020

Highlight Key Issues from Last Cycle and Their Resolution:

- N/A, this is the first review cycle

Concise Description of Outstanding Issues:

- None

B.1 BCS DESIGNATION[1]

Assessment:

The Applicant did not request a BCS designation for the proposed drug product. Fexinidazole exhibits solubility and permeability characteristics consistent with BCS Class II drugs.

Solubility:

Per BCS criteria, fexinidazole is considered to have low solubility. Solubility increased slightly with decreasing pH. [redacted] (b) (4)

Permeability:

The permeability of fexinidazole was characterized using a Caco-2 cell monolayer model in both apical-basolateral (A-B) and the reverse (B-A) direction. The data show that fexinidazole has high permeability.

Dissolution:

The proposed formulation of the drug product is designed to be an immediate-release drug product. The proposed dissolution medium contains 3% sodium lauryl sulfate (SLS) and the proposed drug product contains [redacted] (b) (4) SLS in the [redacted] (b) (4) the formulation.

B.2 DISSOLUTION METHOD

Assessment: *Adequate*

The proposed quality control dissolution method for Fexinidazole tablets uses USP Apparatus II (Paddle) at 75 RPM in 2000 mL of 0.1 N HCl with 3% w/v SLS at 37 ± 0.5 °C. This dissolution method development report was submitted in IND 110365/SDN-18[2] and the proposed method was found to be adequate per the

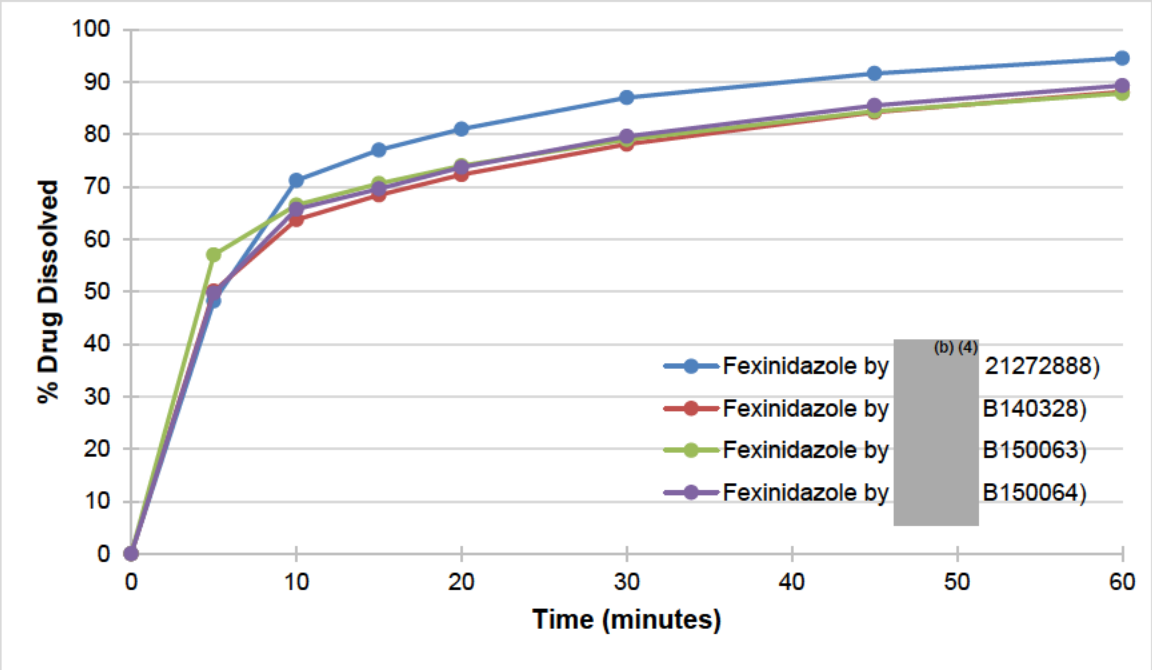
[1] \\CDSESUB1\evsprod\nda214429\0001\m3\32-body-data\32p-drug-prod\fexinidazole-tablet\32p2-pharm-dev\pharmaceutical-development1.pdf

[2] \\CDSESUB1\evsprod\ind110365\0015\m1\us\dissodev-report.pdf

Biopharmaceutics review by Dr. Mathew John, dated February 25, 2020 in DARRTS.[3]

Dissolution Data[4]

Figure 1. Dissolution profiles of Fexinidazole tablets, 600 mg, manufactured at [redacted] using the proposed dissolution method



B.3 DISSOLUTION ACCEPTANCE CRITERION

Assessment: *Adequate*

The originally proposed dissolution acceptance criterion, "NLT [redacted]% (Q) of Fexinidazole in [redacted] minutes," was not found to be acceptable. The provided dissolution data of the registration batches support a dissolution acceptance criterion of "NLT [redacted]% (Q) of Fexinidazole in 60 minutes" for the proposed drug product. An information request was sent on April 27, 2020 to recommend a dissolution acceptance criterion of Q= [redacted]% at 60 minutes. In the response dated May 11, 2020, the Applicant agreed to revise the dissolution acceptance criterion to "NLT [redacted]% (Q) of Fexinidazole in 60 minutes.[5] The finished product batch release and stability specifications were subsequently updated in a response on June 15, 2020.[6]

[3] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8054387c
[4] \\CDSESUB1\evsprod\nda214429\0001\m3\32-body-data\32p-drug-prod\fexinidazole-tablet\32p2-pharm-dev\pharmaceutical-development2.pdf
[5] \\cdsesub1\evsprod\nda214429\0009\m1\us\quality-response-27-apr-2020.pdf
[6] \\CDSESUB1\evsprod\nda214429\0012\m3\32-body-data\32p-drug-prod\fexinidazole-tablet\32p5-contr-drug-prod\32p51-spec\specifications.pdf

B.4 STABILITY

Stability testing was completed on three production scale registration batches (lots B140328, B150063, and B150064) in blister packs with 48 months of long-term (30 °C/75% RH) data and 6 months of accelerated (40 °C/75% RH) data. Stability data for fexinidazole tablets show no significant change in dissolution at (b) (4) minutes under accelerated conditions.[7] However, under long-term conditions, batches B150063 and B150064 displayed faster dissolution with increasing age. A concern was raised regarding the possibility that a faster dissolution could potentially increase the risk of QT prolongation. However, it was determined that faster dissolution at time points prior to 60 minutes is unlikely to have a clinical impact based on the T_{max} of fexinidazole and its metabolites ($\geq$ 4 hours). The observed dissolution trend may be due to decreasing hardness of the tablets with increasing age, however, tablet hardness data were not provided with the stability analysis. This issue was communicated to the Drug Product Reviewer who will determine the necessity of evaluating tablet hardness during stability testing.

B.5 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

Development of Fexinidazole 600 mg Tablets began in (b) (4) with the clinical batch and was then transferred to (b) (4) to scale up for commercial manufacturing. Manufacturing changes from (b) (4) included (b) (4)

A bioequivalence study (DNDiHATFEX008) was conducted to assess whether the registration batches manufactured at (b) (4) were bioequivalent (BE) to the clinical batch manufactured at (b) (4).[8] A single oral dose of 1200 mg fexinidazole (two tablets) was administered to healthy sub-Saharan African male subjects under fed conditions. The 90% confidence interval for C_{max} was 83 – 98% and AUC was 82 – 95%. The Clinical Pharmacology reviewer will evaluate the results of the bioequivalence studies.

Although not required (since a BE study was conducted), comparative dissolution studies were also performed to determine whether the dissolution profile of the clinical batch (manufactured by (b) (4)) is similar to that of the registration batches (manufactured by (b) (4).[9] This Reviewer calculated the similarity factors between the dissolution profile of the clinical batch and the 3 registration batches (f_2 = 58.31, 57.30, 60.48), indicating that the dissolution profiles are similar (f_2 > 50).

[7] \\CDSESUB1\evsprod\nda214429\0001\m3\32-body-data\32p-drug-prod\fexinidazole-tablet\32p8-stab\stability-data.pdf
[8] \\CDSESUB1\evsprod\nda214429\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\dndifex008\study-dndifex008.pdf
[9] \\CDSESUB1\evsprod\nda214429\0001\m2\27-clin-sum\summary-biopharm.pdf

B.6 BIOWAIVER REQUEST

Assessment: *Not Applicable*

A biowaiver is not included nor required.

Primary Biopharmaceutics Assessor's: Churg Chan, Pharm.D.

Secondary Assessor: Elsbeth Chikhale, Ph.D.

APPENDIX I

BIOPHARMACEUTICS LIST OF INFORMATION REQUESTS

The following Information Request (IR) comment was conveyed to the Applicant on April 27, 2020:

> Based on the provided dissolution data a dissolution acceptance criterion of "NLT (b) (4)% (Q) of Fexinidazole in 60 minutes" is recommended. Update your drug product batch release and stability specifications accordingly.

In a response dated May 11, 2020, the Applicant agreed to revise their dissolution acceptance criterion to "NLT (b) (4)% (Q) of Fexinidazole in 60 minutes." In a subsequent response dated June 15, 2020, the Applicant updated their finished product batch release and stability specifications. The response is acceptable.

Churg Chan

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Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 7/29/2020 08:52:41AM
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DOROTA M MATECKA
08/12/2020 06:31:46 PM